REMARKS

The Examiner stated in the Office Action dated June 3, 2003 that the title of the invention is not descriptive since only polynucleotides are presently being claimed. Applicants amended the title to recite "NOVEL HUMAN POLYNUCLEOTIDES". As such, the title is clearly indicative of the invention to which the claims are directed.

The Examiner rejected claims 3 and 10-14 under 35 U.S.C. § 101 due to a lack of patentable utility. The Examiner stated on page 4 of the office action of June 3, 2003 ("Office Action") that the invention lacks a specific, substantial and credible utility, or a well-established utility. However, the Examiner later indicated on page 6 that credible utility of the claimed invention "is not an issue as it is deemed credible that one or more genes may be involved in late stages of stem cell differentiation and development." Applicants are grateful for the Examiner's acknowledgement of the credible utility of the claimed invention. The following remarks address the remaining issues of specific and substantial utility of the claimed invention.

The Examiner contends on page 4 of the Office Action that the claimed polynucleotides lack specific utility because the disclosed uses are generally applicable to broad classes of polynucleotide. According to the guideline, a "specific utility" is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. According to the Guidelines for the Utility Requirement ("Utility Guidelines"), 66 FR 1098 Jan. 5, 2001; MPEP 2107.01, a claim to a polynucloetide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. The Utility Guidelines indicate that since <u>any</u> gene can be used as a "gene probe" or "chromosome marker", there is a lack of specific utility if there is no specific DNA target. Accordingly, any gene or fragment of DNA sequence that is present in the human genome would fall within this broad class of the invention. However, as discussed in the Amendment filed on February 3, 2003, Applicants submit that the gene trap method enriches for a class of genes that are not required for teratocarcinoma cell viability and are likely to be involved in late stages of cellular differentiation and development. As such, the claimed polynucleotides of the present invention can be used as a gene probe or chromosome marker *specific* for such genes that are of particular interest to scientists and medical practitioners studying the

biology of cellular differentiation and development. As clearly set forth by the Federal Circuit in *Carl Zeiss Stiftung v. Renishaw PLC*, 20 USPQ2d 1101 (Fed. Cir. 1991):

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding a lack of utility." *Envirotech Corp. v. Al George, Inc.*, 221 USPQ 473, 480 (Fed. Cir. 1984)

Just because the Applicants have not disclose what precise biological roles do the presently claimed polynucleotides have in the late stages of cellular differentiation and development does not mean that the presently described polynucleotides lack utility.

In fact, Applicants submit that the claimed polynucleotides are specifically identified and functionally validated exons (*i.e.*, exons which had been actually spliced during post-transcriptional processing) that would not have been identified by conventional molecular biology approaches. Exhibit A shows the sequence alignments of SEQ ID NOS:9-18 with human genomic sequences in GenBank. As set forth in the specification, *inter alia*, at page 10, lines 32-33, the present invention provides tools for identifying exon splice junction, chromosome mapping, etc. This is one of the utility of the present invention as set forth throughout the specification as originally filed. The specification, *inter alia*, at page 18, lines 4-7, describes that the claimed polynucleotides from the intron/exon boundaries of the human gene can be used to design primers for use in amplification assays to detect mutations within the exons, introns, splice sites (e.g., splice acceptor and/or donor sites) that can be used in diagnostics. For example, as shown in Exhibit A, Applicants submit that SEQ ID NO:12 defines a coding region since SEQ ID NO:12 spans two distinct exons on chromosome 5 (bases 36474 to 36329; bases 43711 to 43647 from Genbank accession number AC016601.7.1.145264 or bases 16092 to 16237; bases 8875 to 8921 from Genbank accession number AC034246.4.1.155025 which are clones from chromosome 5) that are separated by an intron (bases 36330 to 43710 from Genbank accession number AC016601.7.1.145264 or bases 16238 to 8856 of Genbank accession number AC034246.4.1.155025). SEQ ID NO:16 defines a coding region since SEQ ID NO:16 spans two distinct exons on chromosome 11 (bases 27019 to 26777; bases 37882 to 37722 from Genbank accession number AP003031.3.1.95585 which is a clone from chromosome 11 that are separated by an intron (bases 26776 to 37883 from Genbank accession number

AP003031.31.3.1.95585). SEQ ID NO:17 defines a coding region since SEQ ID NO:17 spans two distinct exons on the X chromosome (bases 9434 to 9761; bases 8124 to 8243 from Genbank accession number AL158141.14.1.184181 which is a clone from the X chromosome) that are separated by an intron (bases 9762 to 8123 from Genbank accession number AL158141.14.1.184181). SEQ ID NO:18 defines a coding region since SEQ ID NO:18 spans two distinct exons on the X chromosome (bases 9434 to 9793; bases 8124 to 8243 from Genbank accession number AL158141.14.1.184181 which is a clone from the X chromosome) that are separated by an intron (bases 9794 to 8123 from Genbank accession number AL158141.14.1.184181).

Applicants point out that only a small percentage (2-4%) of the human genome actually encodes exon sequences, and these exons are widely interspersed within a given chromosome. When the gene comprising these exons are expressed, the cell must clip out these exons and assemble them end-to-end in order to produce a functional mRNA which acts as a template for the translation of a protein product. The claimed polynucleotides comprising the sequence of SEQ ID NOS:9-18 encode exons that are actually spliced together to produce an active functional transcript (*i.e.*, one of the utilities of the described sequences is for defining intron/exon splice-junctions). Exon splice junctions are particularly important in the study of disease and cancer because splice junctions can often be hot spots for erroneous events leading to a disease state. Applicants respectfully submit that the practical scientific value of biologically validated, expressed, and spliced, mRNA sequences is readily apparent to those skilled in the relevant biological art.

In disclosing a functionally validated exon splice junction, the claimed polynucleotides provide physical evidence that effectively trumps the hypothetical conclusions provided by bioinformatics analysis of the corresponding genomic region conducted without supporting physical data. As discussed above, the claimed polynucleotides define intron/exon splice-junctions which produce functional transcripts. Thus, the present sequence clearly meets the requirements of 35 U.S.C. § 101.

Still further, Applicants point out that each of the sequences of the present invention can be used to map a specific region on a specific human chromosome. The specificity of each of the claimed polynucleotides are listed below: SEQ ID NO:9 can be used to map specific exons of human chromosome 1, due to the fact that SEQ ID NO:9 aligns

with two clones from chromosome 1 (Genbank accession numbers AL390242.17.1.68883 and AL158844.14.1.53402); SEQ ID NO:10 can be used to map a specific exon of human chromosome 16, due to the fact that SEQ ID NO:10 aligns with a clone from chromosome 16 (Genbank accession number AC087564 or AC007344); SEQ ID NO:11 can be used to map a specific exon of human chromosome 2, due to the fact that SEQ ID NO:11 aligns with a clone from chromosome 2 (Genbank accession number AC019129); SEQ ID NO:12 can be used to map specific exons of human chromosome 5, due to the fact that SEQ ID NO:12 aligns with two clones from chromosome 5 (Genbank accession number AC016601.7.1.145264 or Genbank accession number AC034246.4.1.155025); SEQ ID NO:13 can be used to map a specific exon of human chromosome 6, due to the fact that SEQ ID NO:13 aligns with a clone from chromosome 6 (Genbank accession number AL391500); SEQ ID NO:14 can be used to map specific exons of human chromosome 13, due to the fact that SEQ ID NO:14 aligns with three clones from chromosome 11 (Genbank accession numbers AL354814.19.1.70126, AL391683.8.1.168373, AL160397.17.1.204056); SEQ ID NO:15 can be used to map a specific exon of human chromosome 11, due to the fact that SEQ ID NO:15 aligns with a clone from chromosome 11 (Genbank accession number AC084117); SEQ ID NO:16 can be used to map specific exons of human chromosome 11, due to the fact that SEQ ID NO:16 aligns with a clone from chromosome 11 (Genbank accession number AP003031.3.1.95585); SEQ ID NO:17 can be used to map specific exons of the human X chromosome, due to the fact that SEQ ID NO:17 aligns with a clone from the X chromosome (Genbank accession number AL158141.14.1.184181); SEQ ID NO:18 can be used to map specific exons of the human X chromosome, due to the fact that SEQ ID NO:18 aligns with a clone from human X chromosome (Genbank accession number AL158141.14.1.184181). Exhibit A shows the sequence alignments of SEQ ID NOS:9-18 with Genbank human genomic sequences. The presently claimed polynucleotides have specific utility in mapping the protein encoding regions of the corresponding human chromosome, as described in the specification, *inter alia*, at page 10, lines 32-33. The exquisite specificity of each of the claimed polynucleotides for their specific locus on a corresponding human chromosome is evidenced by the fact that each of the claimed polynucleotides do not specifically align with any other human genomic sequences. Hence, the claimed polynucleotides are not random fragments of genomic DNA of unknown

location. Thus, the present sequence clearly meets the utility requirements of 35 U.S.C. § 101.

While earlier mapping techniques have identified gross chromosomal positions for numerous disease-associated genes, these techniques are inadequate to precisely map these genes. However, using the presently described nucleotide sequence and a computer system, the exact location of such disease-associated genes is able to be specifically pinpointed, as detailed above. The claimed polynucleotides provide exquisite specificity in localizing the specific region of a particular human chromosome that contains the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present polynucleotides.

Thus, Applicants submit that a polynucleotide of the claimed invention *cannot* be regarded as a gene probe or chromosome marker that is without a target of biological purpose or function. While the asserted utility is not as narrowly defined as that of a correlation with a disease condition, and although the number of polynucleotides that have such a specific utility is relatively larger than that of polynucleotides associated with a Mendelian genetic disease, Applicants submit that, it is nevertheless *not* a general utility that would be applicable to the broad class of genes in the genome. As such, Applicants submits that the claimed invention meets the threshold requirement of having specific utility.

The Examiner contends on page 4 of the Office Action that an adequate nexus cannot be found between the evidence of record and the asserted properties of the claimed subject matter. However, according to the Utility Guidelines, such a nexus is required when the applicants have not asserted any specific and substantial utility for the claimed invention (MPEP 2107). Since the Applicants have asserted specific and substantial utility for the claimed invention, *inter alia*, on page 10, line 32 to page 11, line 11 of the specification, the Examiner is required to establish a *prima facie* case for lack of specific and substantial utility. The Guidelines for the Utility Requirement provides that where the asserted utility is not specific or substantial, a *prima facie* showing must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The *prima facie* showing must contain the following elements (see MPEP 2107(II)(C)(1) and 2107.02(IV)) : (1) an explanation that

clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established; (2) support for factual findings relied upon in reaching this conclusion; and (3) an evaluation of all relevant evidence of record, including utilities taught in the closest prior art. The Examiner has not provided any factual findings in which the conclusion for lack of specific and substantial utility is relied upon, nor has the Examiner evaluated utilities taught in the closest prior art. Accordingly, the Examiner has not provided a *prima facie* showing that the invention does not have specific and substantial utility. The rejection is thus in error and should be withdrawn.

The Examiner contends that Applicants' argument regarding that genes as identified by the method disclosed in the instant specification have a well established utility in the art, specifically, the argument regarding the enrichment of the class of genes that are identified by the present invention, are allegation without factual support. However, Applicants submit that according to MPEP 2107.02(VII), evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. The character and amount of evidence needed to support an asserted utility will vary depending on whether the asserted utility appears to contravene established scientific principles and beliefs. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967); *In re Chilowsky*, 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956). Applicants have provided support derived through scientific logic to show that the gene trap method enriches a class of genes that is involved in late stages of stem cell differentiation and development as discussed in the remarks filed February 3, 2003.

The Examiner further contends that Applicants' argument that the enrichment of a class of genes that are involved in the late stages of stem cell differentiation and development is only a possibility or likelihood and that further research is needed to support this. According to applicable case law, applicants do not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980). The Examiner is apparently questioning the credibility of the statement and not the credibility of utility. However, it is unclear what is the Examiner's basis for disbelieving Applicants' assertion. Applicants

submit that, at least in regard to the requirements to show pharmacological activities for a compound, a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices. *Fujikawa v. Wattanasin*, 93 F.3d 1559; 39 USPQ2d 1897 (Fed. Cir. 1996). In fact, all that is required in evaluating the credibility of an asserted utility is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). A preponderance of the evidence exists when it suggests that it is more likely than not that the assertion is question is true. *Herman v. Huddleston*, 459 U.S.375, 390 (1983). Still further, according to the Utility Guidelines, office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Accordingly, the assertion that the genes identified in the present invention is likely to be involved in the late stages of stem cell differentiation and development absent any countervailing evidence, satisfies the threshold of the utility requirement.

The Examiner contends that when the polynucleotides of the present inventions are used in a microarray to screen for genes that are involved in a particular differentiation stage, the use is for further research and hence lack substantial utility. In the present application, the utility of the claimed invention would be immediately appreciated by those familiar with the technological field of the invention such as biologists studying cellular differentiation and development. Applicants submit that, among other uses, the polynucleotides of the present invention may be used as a research tool in the context of a hybridization assay, e.g., in the format of a microarray. Instead of using the entire universe of genes in the genome in such an experiment, the skilled person has the option of limiting the experiment to using polynucleotides of the invention in the microarray. In effect, genes that are critically essential to the survival and early growth of teratocarcinoma cells would be excluded from the microarray. The use of polynucleotides of the present invention help cut down the number of genes that needs to be studied and simplify the work of a biologist who uses this research tool to study embryonic cell differentiation and development. Thus, no further research is required to identify or reasonably confirm the asserted utility. Applicants submit that the guidelines cautioned not to interpret "immediate benefit to the public" to mean that products or services based on the claimed invention must be "currently available"

to the public in order to satisfy the utility requirement. *Brenner v. Manson*, 383 U.S., 519, 534-35, 148 USPQ 689, 695 (1966). Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility. Here, the set of genes that are enriched for their lack of involvement in cell viability and their likelihood of participating in the late stages of embryonic cell differentiation and their development represents substantial utility to biologists who are studying late stages of cellular differentiation and development. The preselected set of genes are currently available and will immediately provide, at a minimum, the economic benefit of not having to put every gene in the genome on microarray(s). Accordingly, the present invention has substantial utility.

In view of the foregoing, Applicants submit that the utilities of the claimed polynucleotides are specific, substantial and credible. Applicants respectfully request that rejection under 35 U.S.C. § 101 be withdrawn.

Claims 3, and 10-14 are also rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking utility. Applicants submit that when an Applicant satisfactorily rebuts a rejection based on a lack of utility under 35 U.S.C. § 101, the corresponding rejection imposed under 35 U.S.C. §112, first paragraph, should also be withdrawn. Thus, Applicants respectfully request that the rejection of claims 3, and 10-14 under 35 U.S.C.§ 112, first paragraph, be withdrawn.

CONCLUSION

Applicants submit that claims 3, and 10-14 satisfy all of the criteria for patentability and are in condition for allowance. Accordingly, Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application.

Respectfully submitted,

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Enclosures